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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,146	02/04/2002	Frederick P. Siegal	10034-004	7266

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,146	SIEGAL ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,15,21-24,26-30 and 32-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,15,21-24,26-30 and 32-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/09/05 has been entered.

Claims 1-10, 12-14, 16-20, 25 and 31 are canceled.
Claims 11, 15 and 21-24, 26-30 and 32-35 are pending and are examined in this office action

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 11, 15 and 21-24, 26-30 and 32-35 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the same reasons of record as set forth in the office action mailed on 12/03/04.

Nature of Invention:

Invention relates to a method of monitoring the progression of HIV infection or AIDS in a patient by measuring the number of pDC2 cells in lymphoid or blood sample obtained from the patient as compared to a control sample.

Breadth of Claims and Guidance Provided in the Specification

The scope of the invention as claimed encompasses a method of monitoring the progression of HIV infection or AIDS in a patient by measuring number of pDC2 cells obtained from lymphoid tissue or blood sample of a HIV patient and comparing it to a control sample. At best the specification discloses evaluation of IFN-α production by total PBMCs or pDC2-depleted, pDC2-enriched mononuclear cells (pages 30-32). The specification further teaches a method of evaluating the number of pCD2-interferon-producing dendritic cells by cell sorting techniques (fig-1 and 2). The specification further disclosed statistical correlation among IFN-α generation, CD4 T-cell counts and viral burden in HIV patients (page 34, sec.8.2; page 40 table-1). However, the specification as filed fails to establish any correlation between the number of pCD2-interferon-producing dendritic cells and the progression of HIV infection and/or AIDS. Similarly the specification fails to establish the reference range (control sample) for pDC2 cells especially in context HIV infection and/or AIDS, wherein the pDC2 cells has been obtained from any lymphoid tissue or blood sample obtained from the normal subject and HIV patient.

State of Art and Predictability

Interferons are the cytokines produced by virus-infected cells that enable neighboring cells to resist virus infection. IFN-α (leukocyte IFN) and IFN-β (fibroblast IFN), the two type 1 antiviral IFNs, are distinct from type 2 IFN-γ produced by effector T cells. Specialized leukocytes, the "natural IFN-producing cells" (NIPCs), were shown to be the chief IFN-γ producers in response to enveloped viruses, bacteria, and tumor

cells. IPCs express CD4 and major histocompatibility complex (MHC) class II, but lack hematopoietic-lineage markers. Therefore the nature of IPCs, whether they represent dendritic cells or cells of a distinct lineage has been controversial. There is a progressive loss of CD4+ T lymphocytes and functional IPCs during human immunodeficiency virus (HIV) infection. Preservation of IPCs is associated with protection from opportunistic infections, suggesting the importance of IPCs in the host defense (Siegal et al, Science 284:1835-1837, 1999, *ref. of record, see page 1835*). Furthermore, increased frequency and severity of infections in the elderly have been taken as indicative of declining immune function. Dendritic cells (DCs), the most important antigen-presenting cells, play a central role in initiating and modulating immune responses. One type, DC2, arises from precursor plasmacytoid DCs (pDCs), a rare population of circulating blood cells, whose hallmark function is rapid and copious production of interferon- (IFN-α) upon microbial challenge. However there is a significant decrease of the circulating pDCs during ageing in healthy adult humans (Shodell et al Scand J. Imunol 56:518-521, 2002 see page 518). Furthermore the cellular identity of NIPC is the most important issue in the enumeration of NIPC in a particular disease. For example it is important establish whether these cells represent a unique lineage or do they belong to an already defined lineage of cells such as dendritic cells. The developmental pathway of NIPC has not been well characterized. The cellular distribution of NIPC is also not known, since appropriate tissue studies have not been performed to determine whether the cells are able to move out of periphery and into tissues. Clearly most significant impairment to studies of IFN-α system in human peripheral blood remains the inability to identify the unique NIPC (Fitzgerald-Bocarsly et al Pharmac. Ther. 60:39-62, 1993, *ref. of record see page 56 sec.7*).

Response to arguments

Applicant's arguments filed 02/09/05 have been fully considered but they are not persuasive. The applicant argues that method of monitoring the progression of HIV infection or AIDS in a patient and method of assessing the effectiveness of a therapy as claimed are fully enabled. The applicant argues that the meassuring the number of

pDC2 cells in lymphoid tissue or blood sample can be easily done given the instant specification, by simply counting the number of CD4+, CD3- and CD11c- cells. The applicant argues that the specification (table-1) establishes a correlation between the number of pDC2 cells and the progression of AIDS or HIV infection, by measuring interferon production. The applicant argues that the interferon production negatively correlates to with HIV progression and positively correlates to HIV treatment. The applicant argues that the given this data (spec table-1), the skilled artisan would conclude that the quantity of pDC2 cells negatively correlates with HIV disease progression and positively correlates with the effectiveness of HIV treatment. The applicant further argues that this correlation was confirmed in Siegal et al AIDS 15:1603-1612, 2001 and Feldman et al, Clin. Immunol. 101:201-210, 2001. The applicant argues that it would take only routine experimentation to establish controls form any individuals. The applicant concluded that such a determination would not be considered undue experimentation, since there is no uncertainty in the methods used to make those determinations.

However, applicant's arguments are found NOT persuasive because the disclosure "*shall inform how to use, not how to find out how to use for themselves.*" See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). To practice the invention as claimed one skilled in the art needs know i) how to identify a pDC2 cell and ii) establish a range for number of pDC2 expressed in a control sample with or without HIV infection or AIDS. Therefore phenotypic identificaiton of pDC2 cells and number of pDC2 cells in aged matched control samples (with or without HIV infection) is consided germane to practice the instant invention. The specification as filed fails to establish any correlation between the number of pCD2-interferon-producing dendritic cells and the progression of HIV infection and/or AIDS. At best the specification discloses evaluation of IFN-production by total PBMCs or pDC2-depleted, pDC2-enriched mononuclear cells (pages 30-32). The specification fails to provide any direct evidence that establishes there are changes in number of pCD2-interferon-producing dendritic cells during the progression of HIV-infection and upon treatment. In addition the cellular identity of interferon producing cells (IPC) is the key issue in the enumeration of IPC HIV infection and/or

AIDS. For example it is important to establish whether these cells represent a unique lineage or do they belong to an already defined lineage of cells such as dendritic cells. In the instant case the scope of pCD2 phenotype as claimed encompasses a dendritic cells with any phenotype, whereas the instant specification identify the pCD2 cells as $CD4^+$, $CD3^-$, $CD11c^-$ cells. Furthermore as stated above the state of the art teaches that the cellular distribution of pCD2 is not known, since appropriate tissue studies have not been performed to determine whether the cells are able to move out of periphery and into tissues. Therefore the identification of pCD2 phenotype and normal range is considered germane in evaluating the number of pCD2 cells in health or in HIV infection. Furthermore the specification fails to establish the reference range (control sample) for pDC2 cells in context with HIV infection and/or AIDS using aged matched normal healthy individuals. The earlier office action clearly provided the evidence that there is a significant decrease of the circulating pDCs during ageing in healthy adult humans. In addition loss of pDC IFN-a generation by blood MNC attributable not only to declining pDC number but also to the reduction in IFN generated per pDC (see Shodell et al Scand J. Imunol 56:518-521, 2002 . page 519 table 1, page 520, fig-1). Therefore it is highly unpredictable to predict the number of pDC2 (as claimed) by evaluating the levels of IFN-g produced in a sample, since there is considerable variation in the level of interferon produced by pDC2 cell in age related samples. Furthermore considering the state of the art and the limited guidance provided in the instant specification (table-1), it is highly unpredictable to evaluate the progression of HIV infection and/or AIDS based upon number of pDC2 cells as inferred by interferon production alone.

In addition the applicants arguments that Siegal et al AIDS 15:1603-1612, 2001 and Feldman et al, Clin. Immunol. 101:201-210, 2001 supports correlation found in the instant invention, has been found not fully persuasive. At best Siegal 2001 teaches a correlation between the interferon production and HIV disease progression using non-T, HLA-DR blood mononuclear cells known as natural IFN-producing cells (NIPC), which are phenotypically distinct from pDC2 dendritic cells as claimed in the instant invention. Similarly the interferon producing cell population ($lin^-/HLA\text{-}DR^+/CD123^{bright}$) as described by Feldman 2001 is distinct from the interferon producing cell population as disclosed in

the instant application ($CD4^+CD3^-CD11c^-$). Therefore identification of a pDC2 dendritic cell by a well-characterized phenotypic trait is the central dogma, which would enable one skill in the art to exercise the instant invention without further undue amount of experimentation. Applicant's argument alone cannot take place of evidence lacking in the record see In re Scarbrough 182 USPQ, (CCPA) 1979. Each patent application is examined on its own merit and is considered enabled in view of its own disclosure. The issue is not whether the other application support their claims but whether one supports its claims "[i]t is immaterial whether similar claims have been allowed to other" In re Gialito 188USPQ 645,648 (CCPA 1976). At best the specification discloses evaluation of IFN-production by total PBMCs or pDC2-depleted, pDC2-enriched mononuclear cells. The specification as filed fails to establish any correlation between the **number** of pCD2-interferon-producing dendritic cells and the progression of HIV infection and/or AIDS (pages 30-32). Thus the invention as claimed is not enabled in view of limited amount of guidance provided in the instant specification.

In addition monitoring the progression of HIV-infection or AIDS and efficacy of a treatment for AIDS or HIV infection by evaluating the number of pDC2 (any phenotype) in a sample obtained form a blood or any lymphoid tissue of a subject having HIV infection is not considered routine in the art and without sufficient guidance to a specific phenotype of pDC2 cells and correlation of number of pDC2 cells in health and HIV or AIDS, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). Therefore considering the state of the art and limited amount of guidance provided in the instant application one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

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been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300.**

Sumesh Kaushal
Examiner GAU 1636

SUMESH KAUSHAL
PATENT EXAMINER